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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 25

Application Number: 09/486,971
Filing Date: May 19, 2000
Appellant(s): LEHTOLA ET AL.

Gerald M. Murphy
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/16/02.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 3,4,6,11,14-19 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

US 5,525,354	Posti et al.	6-1996
WO 96/21429	Sherwood et al.	8-1996

Remington's Pharmaceutical Sciences, 18th Edition, Mach Publishing Company, 1990, pages 1319 and 1325.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection Under 103

Claims 1, 3-4, 6, 11, 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Posti et al. (US 5525354) in further view of Sherwood (WO 96/21429) and Remington's Pharmaceutical Sciences.

Posti discloses a pharmaceutical preparation for oral use containing a pharmacologically acceptable salt of a dichloromethylene bisphosphonic acid, a clodronate, especially disodium clodronate (see abstract, column 1 lines 6-10). The preparation may also contain additives, such as carriers, diluents, fillers, lubricants, and disintegrating agents, which are all known in the art (see column 2 lines 18-22). More specifically, microcrystalline cellulose as a filler and colloidal silicon dioxide may be used as a lubricant (see column 2 lines 41-51). The preparation is carried out using known tabletting, granulating or pelletization techniques (see column 2 lines 52-54). Example 1 illustrates a tablet comprising disodium clodronate, microcrystalline cellulose and silicon dioxide. The desired amount of clodronate can vary within wide limits from 10 to 95% by weight (see column 2 lines 22-25). The preparation also comprises of microcrystalline cellulose and silicon dioxide comprises about 8 to 20% by weight, and lubricants and/or disintegrants comprise about 0.5 to 10% by weight (see example 1). Posti does not disclose preparing the microcrystalline cellulose and silicon dioxide in a particulate agglomerate of co-processed microcrystalline cellulose and silicon dioxide.

Sherwood discloses a microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation, or wet granulation

formulations. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other (see abstract). Sherwood discloses known methods of tableting. Lubricants are typically added to avoid the material(s) being tabletted from sticking. In addition to lubricants, solid dosage forms often contain diluents. Diluents are frequently added in order to increase the bulk weight of the material to be tabletted in order to make the tablet a practical size for compression. Disintegrants are often included in order to ensure the ultimately prepared compressed solid dosage form has an acceptable disintegrating rate in an environment of use. Typically excipients are added to the formulation, which impart good flow and compression characteristics to the material as a whole. Compared to other directly compressible excipients, microcrystalline cellulose is generally considered to exhibit superior compressibility and disintegration properties (see pages 2 and 4). Sherwood's excipient comprises a particulate agglomerate of copressed microcrystalline cellulose and form about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other (see page 9). Advantages of the disclosed excipient include excellent disintegration properties and improved compressibility (see page 11). By "intimate association", it is meant that the silicon dioxide has in some manner been integrated with the microcrystalline cellulose particles e.g., via a partial coating of the microcrystalline cellulose particles, as opposed to a chemical interaction of the two ingredients. It is most preferred the microcrystalline cellulose and silicon dioxide are coprocessed, resulting in an intimate association of these ingredients, rather than being combined

as a dry mixture. After a uniform mixture of the ingredients is obtained in a suspension, the suspension is dried to provide a plurality of microcrystalline cellulose-based excipient particles having enhanced compressibility. It is preferred that the suspension be dried using spray-drying techniques, as they are known in the art (see page 21).

Remington discloses microcrystalline cellulose as a tablet diluent and disintegrant and silicon dioxide as a tablet diluent and as a suspending and thickening agent in pharmaceutical preparations (see pages 1319 and 1325).

It is the position of the examiner, that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Posti by substituting silicified microcrystalline cellulose taught by Sherwood for the microcrystalline cellulose and silicon dioxide of Posti because of the expectation of achieving excellent disintegration properties and improved compressibility as taught by Sherwood. Remington discloses microcrystalline cellulose and silicon dioxide are known in the art as excipients for tableting, while Sherwood discloses the combination of the two has improved characteristics. Therefore, substituting one excipient, as taught by Sherwood, for two excipients as taught by Posti, would not only have the advantages taught by Sherwood, but would also add convenience to the overall process of making. The expected result would a tablet comprising dicholoromethylene biphosphonic acid and silicified microcrystalline cellulose as the excipient.

(11) Response to Argument

Applicants argue the Examiner has not successfully established *prima facie* obviousness. Applicants assert that the references, taken as a whole, do not suggest the claimed subject matter. Applicants further assert that there is no motivation to combine the teachings of Post, Sherwood and Remington. Another issue is whether Applicants have demonstrated unexpected results.

Applicant's argument: References do not suggest claimed invention.

Applicants argue the essential feature of the Posti reference is the enteric coating. Posti does not provide some motivation or suggestion to prepare the clodronate tablet without the enteric coating. However, Applicants are not claiming the limitation of preparing a tablet without a coating. None of the pending claims are drawn to a non-enteric coated tablet. In fact, in instant claim 16, Applicants claim an optional coating of the tablet. Furthermore, the tablet being claimed by Applicants is not limited to a release rate or specific pH in which the tablet dissolves. Therefore it is unclear to the examiner how the tablet, including an enteric coating of Posti, does not teach the claimed invention.

Applicant's argument; No motivation to combine

Applicants argue while Sherwood teaches the advantages of silicified microcrystalline cellulose to be superior compressibility and disintegrating properties, Sherwood places particular emphasis on wet granulation. Applicants argue neither Posti, nor the present invention utilize wet granulation or direct compression techniques. The examiner refers to Example 1 of Posti, wherein the drug is wet granulated, dried and then mixed with the colloidal silicon dioxide,

croscarmellose sodium and microcrystalline cellulose. The mixture is then wetted with stearic acid and ethanol. Therefore, it is the position of the examiner the primary reference, Posti, teaches wet granulation. Furthermore, Posti discloses the preparation may be carried out using known granulating and tableting techniques, which may be dry or wet granulation, (see Example 1 and col. 2 lines 52-54), while Sherwood discloses the silicified microcrystalline cellulose may be used in direct compression, dry granulation or wet granulation (see abstract). Therefore, the cited references are not limited to wet granulation, but rather teach this process may be used with known granulating and tableting techniques, which include both wet and dry granulation as well as direct compression.

Applicant's arguments: Unexpected results

Applicants argue the friability of the tablets of the instant application is low compared to the tablets as prepared in Posti. The problem is overcome by using silicified microcrystalline cellulose. However, one of ordinary skill in the art would expect that the silicon dioxide in the SMCC would decrease crushing strength and increase friability, which is typical of such gliding agents (see page 4, lines 10-16 of the instant specification). Applicants argue the March 22, 2002 Declaration clearly illustrates the favorable low friability characteristic of the present invention, however, non of the references cited by the examiner disclose the benefit of low friability when preparing clodronate tablets comprising SMCC. Applicants argue the presence of a property not possessed by the prior art is evidence of nonobviousness.

The examiner agrees the prior art is silent to the characteristic of friability. However, it is the position of the examiner the characteristic of friability argued by Applicants is not being

claimed in the instant application. Furthermore, the scope of the Declaration is not commensurate in scope with the instance claims. Specifically, Batch 1 discloses a tablet comprising anhydrous disodium clodronate, silicified microcrystalline cellulose, croscarmellose sodium, stearic acid, and magnesium stearate and Batch 3 discloses disodium clodronate, providone, croscarmellose sodium, silicified microcrystalline cellulose, lactose monohydrate, stearic acid, colloidal anhydrous silicon dioxide, talc and magnesium stearate, while the instant claims 1, 3, 4, 6, 11, 14 are drawn a tablet comprising anhydrous disodium clodronate, silicified microcrystalline cellulose and lubricants and/or disintegrants. Thus, the rejection is proper because the friability characteristic and the specific compositions, ingredients and amounts, disclosed in Batches 1 and 3 of the Declaration are not being claimed by Applicants.

In response to Applicants argument there is no motivation of combining the cited references, the examiner refers to Sherwood, wherein the motivation to substitute silicified microcrystalline cellulose for microcrystalline cellulose and silicone dioxide is taught by Sherwood on page 11. The advantages disclosed by Sherwood include excellent disintegration properties and improved compressibility. Although the motivation is not for the same reason Applicant is arguing, the rejection is still proper.

Conclusion

The primary reference, Posti '354, teaches the active ingredient, the specific amounts, and the excipients microcrystalline cellulose and silicone dioxide. The method of manufacturing is disclosed in Example 1 of Posti' 354. The secondary references, Sherwood (WO 96/21429) and Remington's Pharmaceutical Science, are added to show the excipient,

silicified microcrystalline cellulose (SMCC-which is microcyrstalline cellulose and silicon dioxide in an intimate association with each other) may be substituted for the microcyrstalline cellulose and silicone dioxide. The motivation for such a substitution is found in the secondary references, specifically Sherwood wherein Sherwood's excipient comprises a particulate agglomerate of copressed microcrystalline cellulose and form about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other (see page 9). Advantages of the disclosed excipient include excellent disintegration properties and improved compressibility (see page 11). By "intimate association", it is meant that the silicon dioxide has in some manner been integrated with the microcrystalline cellulose particles e.g., via a partial coating of the microcrystalline cellulose particles, as opposed to a chemical interaction of the two ingredients. Therefore, the rejection has been maintained because there is reasonable motivation for one of ordinary skill in the art to substitute the excipient taught by Sherwood for the excipients taught by Posti because Remington discloses microcrystalline cellulose and silicon dioxide are known in the art as excipients for tableting, while Sherwood discloses the combination of the two has improved characteristics such as excellent disintegration properties and improved compressibility. Therefore, substituting one excipient, as taught by Sherwood, for two excipients as taught by Posti, would not only have the advantages taught by Sherwood, but would also add convenience to the overall process of making.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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January 10, 2003

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